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<p>(54) Title: METHODS AND COMPOSITIONS FOR TREATING GASTRIC DISORDERS USING OPTICALLY PURE (+) PANTOPRAZOLE</p> <p>(57) Abstract</p> <p>Methods and compositions are disclosed utilizing optically pure (+) pantoprazole for the treatment of ulcers in humans while substantially reducing the concomitant liability of adverse effects associated with the racemic mixture of pantoprazole. The optically pure (+) isomer is also useful for the treatment of gastroesophageal reflux. (+) Pantoprazole is an inhibitor of H⁺ release and is therefore useful in the treatment of other conditions related to gastric hypersecretion such as Zollinger-Ellison Syndrome.</p>		

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-1-

METHODS AND COMPOSITIONS FOR TREATING GASTRIC
DISORDERS USING OPTICALLY PURE (+) PANTOPRAZOLE

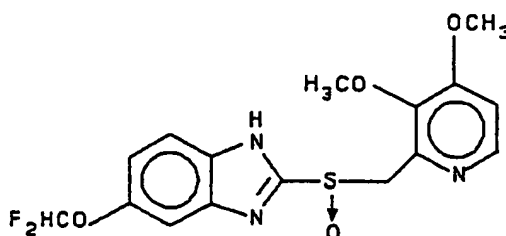
BACKGROUND OF THE INVENTION

5 This invention relates to novel compositions of
matter containing optically pure (+) pantoprazole.
These compositions possess potent activity in
treating ulcers of the stomach, duodenum and
esophagus, gastroesophageal reflux diseases,
Zollinger-Ellison Syndrome, and other disorders
10 including those that would benefit from an inhibitory
action on gastric acid secretion. (+) Pantoprazole
inhibits the H^+ , K^+ -ATPase associated with the gastric
proton pump and the resulting secretion of gastric
acid by parietal cells providing therapy in diseases
15 associated with gastric hyperacidity. Optically
pure (+) pantoprazole provides this treatment while
substantially reducing adverse effects, including,
but not limited to, hepatocellular neoplasia, gastrin
hypersecretion, gastric neoplasms or carcinoids,
20 headache, diarrhea and skin alterations which are
associated with the administration of the racemic
mixture of pantoprazole. Also disclosed are methods
for treating the above described conditions in a
human while substantially reducing the adverse
25 effects that are associated with the racemic mixture
of pantoprazole by administering the (+) isomer of
pantoprazole to said human.

The active compound of these compositions and
methods is an optical isomer of pantoprazole. The
30 preparation of racemic pantoprazole is described in
United States Patent No. 4,758,579. The medicinal

-2-

chemistry of pantoprazole is described by Kohl et al. [J. Med. Chem. 35, 1049-1057 (1992)], Kromer et al. [J. Pharm. Exp. Ther. 254, 129-135 (1990)], Simon et al. [Aliment. Pharmacol. Therap. 4, 239-245 (1990)],
5 Beil et al. [Europ. J. Pharmacol. 218, 265-271 (1992)], and Kromer et al. [Pharmacology 41, 333-337 (1990)]. Chemically, the active compound is the (+) isomer of 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole(I),
10 hereinafter referred to as pantoprazole.



I

(+) Pantoprazole, which is the subject of the present invention, is not presently commercially available; only the 1:1 racemic mixture is
15 commercially available as its sodium salt.

Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The
20 prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with
25

-3-

(+) or d is dextrorotatory. There is no correlation between nomenclature for the absolute stereochemistry and for the rotation of an enantiomer. Thus, D-lactic acid is the same as (-) lactic acid, and L-lactic acid is (+). For a given chemical structure, these chiral compounds exist as a pair of enantiomers which are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric or racemic mixture.

Stereochemical purity is of importance in the field of pharmaceuticals, where 12 of the 20 most prescribed drugs exhibit chirality. A case in point is provided by the L-form of the beta-adrenergic blocking agent, propranolol, which is known to be 100 times more potent than the D-enantiomer.

Furthermore, optical purity is important since certain isomers may actually be deleterious rather than simply inert. For example, it has been suggested that the D-enantiomer of thalidomide was a safe and effective sedative when prescribed for the control of morning sickness during pregnancy, while the corresponding L-enantiomer has been believed to be a potent teratogen.

The separation of racemic pantoprazole into (+) pantoprazole and (-) pantoprazole is described in German application 4,035,455, but no pharmacology of the individual enantiomers is reported.

-4-

Racemic pantoprazole had been in clinical trials in Europe and the United States under the sponsorship of two pharmaceutical manufacturers, but the United States and British sponsor withdrew in 1991 due to
5 concerns about hepatocellular neoplasia seen in rats in a two year carcinogenicity study. Trials continue in Europe and initial reports indicate 90-100% ulcer healing in patients suffering from duodenal ulcers after four weeks of 20 to 80 mg of racemic
10 pantoprazole per day.

Racemic pantoprazole sodium is an orally active, potent, irreversible inhibitor of H^+,K^+ -ATPase. The compound is one of the class of compounds known as gastric "proton pump" inhibitors. These compounds
15 are weak organic bases which diffuse passively from the plasma into the acid-containing intracellular canaliculi of gastric parietal cells. At the low pH found in the lumen of these canaliculi, the protonated compounds rearrange to form pyridinium
20 sulfenamides, which react with sulfhydryl groups present on the ATPase localized in the membranes lining the intracellular canaliculi. The alkylation of the sulfhydryl inhibits the ability of the enzyme to catalyze the secretion of H^+ into the lumen in
25 exchange for K^+ ions. This inhibition results in an overall reduction in hydrochloric acid secretion by the parietal cells into the cavity of the stomach, thus increasing intragastric pH. As a consequence of reduced acidity in the stomach, the activity of the
30 proteolytic enzyme pepsin is also markedly decreased. Because the proton pump is the final step in acid production and the compounds of this class combine covalently with the associated H^+,K^+ -ATPase, a

-5-

profound and prolonged inhibition of gastric acid secretion can be achieved.

The potency of pantoprazole in vitro as an inhibitor of aminopyrine uptake, which is an index of acid secretion in isolated gastric glands, is similar to that of omeprazole, a structurally related antiulcer agent. Pantoprazole is, however, more chemically stable under neutral and moderately acidic conditions than is omeprazole. This may increase pantoprazole's selectivity for the acid secreting parietal cells, where low pH conditions exist in the intracellular canaliculi. In intact animals, pantoprazole is active in inhibiting gastric acid secretion in both rats and dogs. Specifically, the intravenous and oral doses required to reduce endogenous acid secretion in pylorus-ligated rats by 50% are in the 1-3 $\mu\text{mole/kg}$ range. The calculated oral/intravenous (p.o./i.v.) ratio is approximately 2, suggesting good oral bioavailability. Racemic pantoprazole is also effective at doses less than 5 $\mu\text{mole/kg}$ in inhibiting exogenously stimulated acid secretion induced by a variety of agonists, indicating general activity of the drug in inhibiting acid secretion. The serum half-life of racemic pantoprazole is 1.1 to 1.5 hours in humans. Compared to omeprazole, racemic pantoprazole is a weaker inhibitor of hepatic drug metabolizing enzyme systems in intact rats and rat microsomal enzyme preparations. The intravenous LD_{50} values are 632 (rat) and 975 (mice) $\mu\text{mole/kg}$; oral LD_{50} in mice is 1,893 and in rats $> 2,467 \mu\text{mol/kg}$. The p.o./i.v. LD_{50} ratio of the compound in mice is about 2 and the rat LD_{50} values are at least two to three orders of

-6-

magnitude greater than the corresponding doses required to produce half-maximal inhibition of endogenous acid secretion in this species.

5 Although no cardiovascular or obvious physical changes have been observed in humans on short-term administration of racemic pantoprazole, fasting serum gastrin levels are significantly elevated. This is cause for concern because prolonged elevated serum
10 gastrin appears to be associated with diffuse and focal enterochromaffin-like cell hyperplasia and focal neoplasia (carcinoids) in rats. [Larsson et al. Gastroenterology 90, 391-399 (1986)]. Thus, despite its advantages, some adverse effects of
15 racemic pantoprazole may remain, including, but not limited to, some incidence of hepatocellular neoplasia and gastric carcinoids on long-term therapy, and headache, diarrhea and skin alterations on acute therapy. It would therefore be particularly
20 desirable to find a compound with the advantages of the racemic mixture of pantoprazole which would not have the aforementioned disadvantages.

SUMMARY OF THE INVENTION

25 It has now been discovered that the optically pure (+) isomer of pantoprazole is an effective agent for treating ulcers of the stomach, duodenum and esophagus, gastroesophageal reflux diseases, Zollinger-Ellison Syndrome and other disorders, including those that would benefit from an inhibitory
30 action on H^+, K^+ -ATPase. The optically pure (+) isomer of pantoprazole provides this effective treatment while substantially reducing the adverse effects of

-7-

racemic pantoprazole including, but not limited to, hepatocellular neoplasia, gastric carcinoids, headache, diarrhea and skin alterations. The present invention also includes methods for treating the
5 above described conditions in a human while substantially reducing the adverse effects that are associated with the racemic mixture of pantoprazole by administering the optically pure (+) isomer of pantoprazole to said human.

10 DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of treating ulcers, which comprises administering to a human in need of such therapy, an amount of (+) pantoprazole, or a pharmaceutically acceptable salt
15 thereof, substantially free of its (-) stereoisomer, said amount being sufficient to alleviate the symptoms of ulcers. The method substantially reduces the concomitant liability of adverse effects associated with the administration of the racemic
20 compound by providing an amount which is insufficient to cause the adverse effects associated with the racemic mixture of pantoprazole.

The present invention also encompasses an
25 antiulcer composition for the treatment of a human in need of antiulcer therapy, which comprises an amount of (+) pantoprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to
30 alleviate said ulcers. Preferably the amount is insufficient to cause the adverse effects associated with racemic pantoprazole.

-8-

The present invention further encompasses a method of treating gastroesophageal reflux disease in a human, which comprises administering to a human in need of such therapy, an amount of (+) pantoprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, sufficient to alleviate said gastroesophageal reflux. The method substantially reduces the concomitant liability of adverse effects associated with the administration of racemic pantoprazole by providing an amount which is insufficient to cause adverse effects associated with the administration of racemic pantoprazole.

In addition, the present invention encompasses a composition for the treatment of a human having gastroesophageal reflux disease, which comprises an amount of (+) pantoprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (-) isomer, said amount being sufficient to alleviate or palliate said disorder. Preferably the amount is insufficient to cause adverse effects associated with the administration of racemic pantoprazole.

A further aspect of the present invention includes a method of treating a condition caused by or contributed to by gastric hypersecretion in a human, which comprises administering to a human in need of such therapy, an amount of (+) pantoprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, sufficient to alleviate said gastric hypersecretion. The method substantially reduces the concomitant liability of adverse effects associated with the

-9-

administration of racemic pantoprazole by providing an amount which is insufficient to cause adverse effects associated with the administration of racemic pantoprazole. Conditions associated with
5 hypersecretion in humans may include, but are not limited to, Zollinger-Ellison syndrome.

In addition, the invention encompasses a composition for the treatment of a condition caused by or contributed to by gastric hypersecretion in a
10 human which comprises an amount of (+) pantoprazole or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, the amount being sufficient to alleviate the condition. Preferably the amount is insufficient to
15 cause adverse effects associated with the administration of racemic pantoprazole.

The available racemic mixture of pantoprazole (i.e., a 1:1 racemic mixture of the two enantiomers) exhibits antiulcer activity through its selective,
20 potent, and irreversible inhibition of H^+, K^+ -ATPase, thus providing therapy and a reduction of symptoms in a variety of conditions and disorders related to hypersecretion; however, this racemic mixture, while offering the expectation of efficacy, causes adverse
25 effects which are serious enough to have caused curtailment of clinical trials. Utilizing the optically pure or substantially optically pure isomer of (+) pantoprazole results in enhanced efficacy, diminished adverse effects, and accordingly, an
30 improved therapeutic index. It is therefore, more desirable to use the (+) isomer of pantoprazole than to administer the racemic mixture.

-10-

The term "adverse effects" includes, but is not limited to, hepatocellular neoplasia, gastrin hypersecretion, gastric carcinoids, headache, diarrhea and skin alterations.

5 The term "substantially free of its (-) stereoisomer" as used herein means that the compositions contain at least 90% by weight of (+) pantoprazole and 10% by weight or less of (-) pantoprazole. In a more preferred embodiment the term
10 "substantially free of the (-) isomer" means that the composition contains at least 99% by weight of (+) pantoprazole, and 1% or less of (-) pantoprazole. In the most preferred embodiment, the term "substantially free of its (-) stereoisomer" as used
15 herein means that the composition contains greater than 99% by weight of (+) pantoprazole. These percentages are based upon the total amount of pantoprazole in the composition. The terms "substantially optically pure (+) isomer of
20 pantoprazole" or "substantially optically pure (+) pantoprazole" and "optically pure (+) isomer of pantoprazole" and "optically pure (+) pantoprazole" are also encompassed by the above-described amounts.

25 The term "treating ulcers" as used herein means treating, alleviating or palliating such conditions, and thus providing relief from the symptoms of nausea, heartburn, post-prandial pain, vomiting, and diarrhea.

30 The term "a method for treating gastroesophageal reflux diseases in a human" as used herein means treating, alleviating or palliating the conditions

-11-

that result from the backward flow of the stomach contents into the esophagus.

The term "treating a condition caused, or contributed to, by gastric hypersecretion in a human" as used herein means treating, alleviating or palliating such disorders associated with hypersecretion, thus providing relief from the symptoms of the aforementioned conditions. Zollinger-Ellison Syndrome is among the conditions caused by or contributed to by hypersecretion.

The chemical synthesis of the racemic mixture of pantoprazole can be performed by the method described in U.S. Patent 4,758,579 cited above. The (+) isomer of pantoprazole may then be obtained from its racemic mixture by resolution of the enantiomers of pantoprazole or precursors thereto using conventional means such as an optically active resolving base. German application 4,035,455 (Kohl et al.), which is incorporated herein by reference, discloses a method for resolving the racemic pantoprazole by forming an alkoxymethylamine with fenchyl chloromethyl ether. Other standard methods of resolution known to those skilled in the art including, but not limited to, simple crystallization and chromatographic resolution, can also be used. (See for example, E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw Hill (1962) and [Wilen and Lochmuller "Tables of Resolving Agents" Journal of Chromatography 113, 283-302 (1975)]. Alternatively, the prochiral sulfide may be enantiospecifically oxidized to the (+) sulfoxide by processes known in the art.

-12-

The magnitude of a prophylactic or therapeutic dose of (+) pantoprazole in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose and perhaps the dose frequency will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range for (+) pantoprazole for the conditions described herein is from about 5.0 mg to about 125 mg in single or divided doses. Preferably a daily dose range should be about 10 mg to about 100 mg in single or divided doses while most preferably a daily dose range should be about 20 mg to about 80 mg in single or divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps at about 10 mg to about 25 mg and increased up to about 80 mg or higher depending on the patient's global response. It is further recommended that children and patients over 65 years and those with impaired renal or hepatic function, initially receive low doses, and that they be titrated based on individual response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response. The terms "an amount sufficient to alleviate or palliate ulcers but insufficient to cause said adverse effects," "an amount sufficient to alleviate the symptoms of gastroesophageal reflux but insufficient to cause said adverse effects," and "an amount sufficient to alleviate gastric hypersecretion

-13-

but insufficient to cause said adverse effects" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of (+) pantoprazole. For example, oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, and like forms of administration may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like.

The pharmaceutical compositions of the present invention comprise (+) pantoprazole as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic bases. Since the compound of the present invention is a weak acid ($pK_a = 8.2$), salts may be prepared from pharmaceutically acceptable non-toxic bases including inorganic and organic bases. Suitable pharmaceutically acceptable base addition salts for the compound of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-

-14-

methylglucamine) and procaine. Sodium salts are particularly preferred.

The compositions of the present invention include suspensions, solutions, elixirs, aerosols, or
5 solid dosage forms. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in
10 the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral
15 dosage unit forms, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and
20 delivery devices such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions of the present
25 invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or aerosol sprays, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension
30 in an aqueous liquid, a non-aqueous liquid, an oil-

-15-

in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient
5 with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if
10 necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be
15 prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made by
20 molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 10 mg to about 100 mg of the active ingredient, and each cachet or capsule contains from about 10 mg to
25 about 100 mg of the active ingredient. Most preferably, the tablet, cachet or capsule contains either one of three dosages, about 20 mg, about 40 mg or about 80 mg of (+) pantoprazole sodium salt for oral administration.

30 The invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the present

-16-

invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and
5 interest of this invention.

EXAMPLES

Example 1

The relative activity, potency and specificity of optically pure pantoprazole and racemic
10 pantoprazole both as gastric antisecretory agents and plasma gastrin elevating agents can be determined by a pharmacological study in animals according to the method of Decktor et al. [J. Pharmacol. Exp. Ther. 249, 1-5 (1989)]. The test provides an estimate of
15 relative activity, potency and, through a measure of specificity, an estimate of therapeutic index. Fasted rats, implanted with a gastric cannula, receive single oral or parenteral doses of (+) pantoprazole, (-) pantoprazole or racemate, 1 hour
20 before collection of gastric juice over a four hour period. Acid output and pH are then determined on each sample. Dose response evaluations are performed with each compound to determine the lowest dose which inhibits acid output by at least 95% and maintains
25 gastric pH above 7.0. Plasma gastrin levels are then determined in a second group of rats treated with the doses selected in the first series of tests. Blood samples are taken for analyses over the five hour period after dosing, and both peak level as well as
30 area-under-the-curve analyses of the gastrin responses are made. These responses are then

-17-

analyzed statistically using Student's "t" test to assess whether equivalent antisecretory doses show differences in gastrin responses.

Example 2

5

ORAL FORMULATION

Capsules:

Formula	Quantity per capsule in mg		
	A	B	C
10 (+) Pantoprazole sodium salt	20	40	80
Lactose	152	132	142
Cornstarch	27.5	27.5	27.5
Magnesium Stearate	0.50	0.50	0.50
15 Compression Weight	200	200	250

20 The (+) pantoprazole, lactose and cornstarch are blended until uniform and then the magnesium stearate is blended into the resulting powder, which is sieved and filled into suitably sized, two-piece, hard gelatin capsules using conventional machinery. Other doses may be prepared by altering the fill weight
25 and, if necessary, changing the capsule size to suit.

-18-

Example 3
ORAL FORMULATION

Tablets:

5	Formula	Quantity per tablet in mg		
		A	B	C
	(+) Pantoprazole sodium salt	20	40	80
	Lactose	147	127	137
10	Cornstarch	5	5	5
	Water (per thousand Tablets)*	48 mL	48 mL	48 mL
	Cornstarch	27.5	27.5	27.5
15	Magnesium Stearate	0.50	0.50	0.50
	Compression Weight	200	200	250

*The water evaporates during manufacture

- 20 The (+) pantoprazole is blended with the lactose until a uniform blend is formed. The smaller quantity of cornstarch is blended with the water to form the resulting corn starch paste. This is then mixed with the uniform blend until a uniform wet mass
- 25 is formed. The remaining cornstarch is added to the resulting wet mass and mixed until uniform granules are obtained. The granules are then screened through a suitable milling machine, using a 1/4 inch
- 30 stainless steel screen. The milled granules are dried in a suitable drying oven until the desired moisture content is obtained. The dried granules are

-19-

then milled through a suitable milling machine, magnesium stearate is blended in, and the resulting mixture is compressed into tablets of the desired shape, thickness, hardness and disintegration.

- 5 Tablets of other strengths may be prepared by altering the ratio of active ingredient to the excipients or to the final weight of the tablet. An enteric coating, such as the polyacrylate Eudragit L® and Eudragit S® series, is applied by spray coating
- 10 the tablets, preferably with an aqueous dispersion of the coating polymer.

-20-

What is claimed is :

1. A method of treating ulcers in a human which comprises administering to said human an amount of (+) pantoprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to alleviate or palliate said ulcers.
2. The method of claim 1 wherein (+) pantoprazole is administered parenterally, transdermally, or orally as a tablet or a capsule.
3. The method of claim 2 wherein the amount of (+) pantoprazole or a pharmaceutically acceptable salt thereof administered is from about 5 mg to about 125 mg per day.
4. The method of claim 3 wherein the amount administered is from about 10 mg to about 100 mg per day.
5. The method of claim 4 wherein the amount administered is from about 20 mg to about 80 mg per day.
6. The method of claim 1 wherein the amount of (+) pantoprazole or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total weight of pantoprazole.
7. The method of claim 1 wherein the amount of said (+) pantoprazole or a pharmaceutically acceptable salt thereof, substantially free of its

-21-

(-) stereoisomer, is administered together with a
5 pharmaceutically acceptable carrier.

8. The method according to claim 1, wherein
(+) pantoprazole is administered as a sodium salt.

9. A method of treating ulcers in a human
while substantially reducing the concomitant
liability of adverse effects associated with racemic
pantoprazole which comprises administering to a human
5 in need of such antiulcer therapy an amount of (+)
pantoprazole, or a pharmaceutically acceptable salt
thereof, substantially free of its (-) stereoisomer,
said amount being sufficient to alleviate or palliate
said ulcers but insufficient to cause said adverse
10 effects.

10. A pharmaceutical composition for the
treatment of a human in need of ulcer therapy which
comprises an amount of (+) pantoprazole or a
pharmaceutically acceptable salt thereof,
5 substantially free of its (-) stereoisomer, said
amount being sufficient to alleviate said ulcers.

11. The composition of claim 10 wherein said
amount of (+) pantoprazole is sufficient to alleviate
ulcers but insufficient to cause adverse effects
associated with the administration of racemic
5 pantoprazole.

12. The composition according to claim 10
wherein (+) pantoprazole is administered as a sodium
salt.

-22-

13. The composition according to claim 10 adapted for oral administration.

14. The composition according to claim 10 adapted for parenteral delivery.

15. The composition according to claim 10 wherein (+) pantoprazole or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, is administered together with a
5 pharmaceutically acceptable carrier.

16. A method of treating gastroesophageal reflux disease in a human which comprises administering to said human an amount of (+) pantoprazole, or a pharmaceutically acceptable salt
5 thereof, substantially free of its (-) stereoisomer, said amount being sufficient to alleviate symptoms of gastroesophageal reflux.

17. The method of claim 16 wherein (+) pantoprazole is administered parenterally, transdermally, or orally as a tablet or a capsule.

18. The method of claim 17 wherein the amount of (+) pantoprazole or a pharmaceutically acceptable salt thereof administered is from about 5 mg to about 125 mg per day.

19. The method of claim 18 wherein the amount administered is from about 10 mg to about 100 mg per day.

-23-

20. The method of claim 19 wherein the amount administered is from about 20 mg to about 80 mg per day.

21. The method of claim 16 wherein the amount of (+) pantoprazole or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total weight of pantoprazole.

22. The method of claim 16 wherein the amount of said (+) pantoprazole or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, is administered together with a
5 pharmaceutically acceptable carrier.

23. The method according to claim 16, wherein (+) pantoprazole is administered as a sodium salt.

24. A method of treating gastroesophageal reflux disease in a human, while substantially reducing the concomitant liability of adverse effects associated with racemic pantoprazole, which comprises
5 administering to a human in need of such therapy an amount of (+) pantoprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to alleviate symptoms of gastroesophageal reflux but
10 insufficient to cause said adverse effects.

25. A pharmaceutical composition for the treatment of a human in need of therapy for gastroesophageal reflux disease which comprises an amount of (+) pantoprazole or a pharmaceutically
5 acceptable salt thereof, substantially free of its

-24-

(-) stereoisomer, said amount being sufficient to alleviate said gastroesophageal reflux.

26. The composition of claim 25 wherein said amount of (+) pantoprazole is insufficient to cause adverse effects associated with the administration of racemic pantoprazole.

27. The composition according to claim 25 wherein (+) pantoprazole is administered as a sodium salt.

28. The composition according to claim 25 adapted for oral administration.

29. The composition according to claim 25 adapted for parenteral delivery.

30. The composition according to claim 25 wherein (+) pantoprazole or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, is administered together with a
5 pharmaceutically acceptable carrier.

31. A method of treating a condition caused by or contributed to by gastric hypersecretion in a human which comprises administering to said human an amount of (+) pantoprazole, or a pharmaceutically
5 acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to alleviate said gastric hypersecretion.

32. The method according to claim 31 wherein said condition is Zollinger-Ellison Syndrome.

-25-

33. The method of claim 31 wherein (+) pantoprazole is administered parenterally, transdermally, or orally as a tablet or a capsule.

34. The method of claim 33 wherein the amount of (+) pantoprazole or a pharmaceutically acceptable salt thereof administered is from about 5 mg to about 125 mg per day.

35. The method of claim 34 wherein the amount administered is from about 10 mg to about 100 mg per day.

36. The method of claim 35 wherein the amount administered is from about 20 mg to about 80 mg per day.

37. The method of claim 31 wherein the amount of (+) pantoprazole or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total weight of pantoprazole.

38. The method of claim 31 wherein the amount of said (+) pantoprazole or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, is administered together with a
5 pharmaceutically acceptable carrier.

39. The method according to claim 31, wherein (+) pantoprazole is administered as a sodium salt.

40. A method of treating a condition caused by or contributed to by gastric hypersecretion in a human, while substantially reducing the concomitant

-26-

liability of adverse effects associated with racemic
5 pantoprazole, which comprises administering to a
human, in need of such therapy, an amount of (+)
pantoprazole, or a pharmaceutically acceptable salt
thereof, substantially free of its (-) stereoisomer,
said amount being sufficient to alleviate said
10 gastric hypersecretion but insufficient to cause said
adverse effects.

41. A composition for the treatment of a
condition caused by or contributed to by gastric
hypersecretion in a human which comprises an amount
of (+) pantoprazole or a pharmaceutically acceptable
5 salt thereof, substantially free of its (-)
stereoisomer, said amount being sufficient to
alleviate said condition.

42. The composition of claim 41 wherein said
amount of (+) pantoprazole is insufficient to cause
adverse effects associated with the administration of
racemic pantoprazole.

43. The composition according to claim 41
wherein said condition is Zollinger-Ellison Syndrome.

44. The composition according to claim 41
wherein (+) pantoprazole is administered as a sodium
salt.

45. The composition according to claim 41
adapted for oral administration.

46. The composition according to claim 41
adapted for parenteral delivery.

-27-

47. The composition according to claim 41 wherein (+) pantoprazole or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer; is administered together with a
5 pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/04575

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/44

US CL :514/338

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/338

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS- OMEPRAZOLE, PANTOPRAZOLE, ENANTIOMERS AND ULCERS, GASTROESOPHAGEAL REFLUX, GASTRIC HYPERSECRETION, GASTRIC OR INTESTINAL DISORDERS AND ZOLLINGER-ELLISON SYNDROME

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US, A, 4,758,579 (KOHL ET AL.) 19 JULY 1988, SEE ESPECIALLY THE ABSTRACT, COLUMN 12, LINES 1-11, COLUMN 30, LINES 52-62, COLUMN 31, LINES 21-29 AND 38-52 AND CLOUMN 36, CLAIM 36.	10-15, 25-30, 41-47 ----- 1-9, 16-24, 31-40
X --- Y	DE, A, 4,035,455 (BYK GULDEN LOMBERG CHEM FAB) 14 MAY 1992, SEE ABSTRACT AND PAGES 7-8.	31-47 ----- 1-30
Y	BERKOW ET AL., "THE MERCK MANUAL" (VOL. 1, 15 TH ED.), PUBLISHED 1987 BY MERCK SHARP AND DOHME RESEARCH LABORATORIES (N.J.), SEE PAGES 556-7, AND 570-2.	1-47



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* Inter document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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29 JUL 1994

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